PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 491/052, A61K 31/415, 31/35

A1

(11) International Publication Number: **WO 95/27714**

(43) International Publication Date: 19 October 1995 (19.10.95)

(21) International Application Number: PCT/SE95/00376

(22) International Filing Date: 7 April 1995 (07.04.95)

(30) Priority Data:
9401197-0 11 April 1994 (11.04.94) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BRIVING, Carin, Birgitta [SE/SE]; Nyländningen 2, S-427 34 Billdal (SE). NORDBERG, Mats, Peter [SE/SE]; Björkebergsvägen 9, S-433 60 Sävedalen (SE). STARKE, Carl, Ingemar [SE/SE]; Frigångsgatan 8 C, S-413 01 Göteborg (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

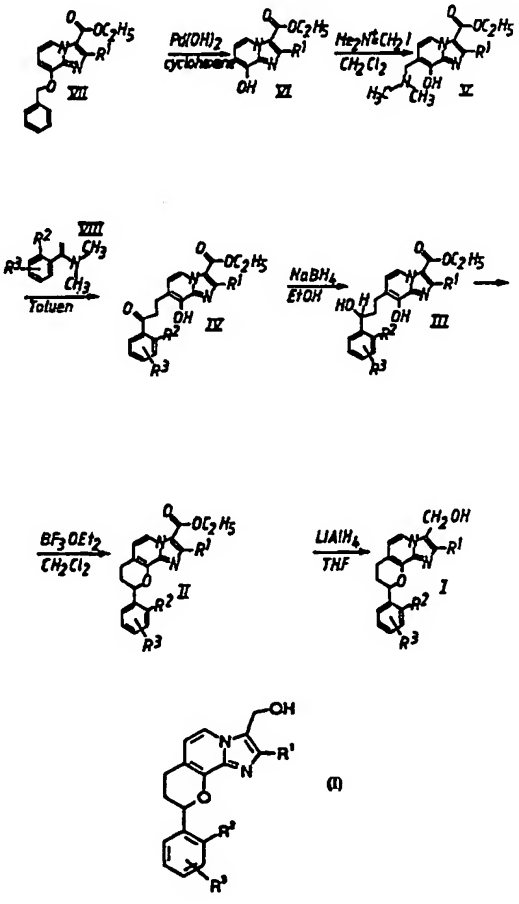
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: ACTIVE COMPOUNDS

(57) Abstract

The present invention relates to substituted tricyclic imidazo[1,2-a]pyridines of formula (I) which reversibly inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

ACTIVE COMPOUNDS

TECHNICAL FIELD

The present invention relates to novel compounds, and therapeutically acceptable salts thereof, which reversibly inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known from publications, hereinafter referred to as "D1" to "D5", by J. J. Kaminski et al. in the Journal of Medical Chemistry:

D1	J. Med. Chem. vol. 28, 876-892, 1985
D2	J. Med. Chem. vol. 30, 2031-2046, 1987
D3	J. Med. Chem. vol. 30, 2047-2051, 1987
D4	J. Med. Chem. vol. 32, 1686-1700, 1989
D5	J. Med. Chem. vol. 34, 533-541, 1991

In D1, the representative compound 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (compound 27 of D1; subsequently designated "Sch 28080") was prepared. When tested for inhibition of

histamine-stimulated gastric acid secretion in dogs, this compound had an ED_{50}-value of 4.4 mg/kg, equivalent to 15.9 μmol/kg (oral administration). In comparison, the compound 3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (compound 80 of D1) gave only 43% inhibition when 8 mg/kg (29.8 μmol/kg) was administered. From these and other experiments, the conclusion was drawn that the 3-cyanomethyl substituent is almost uniquely effective in imparting inhibition of gastric acid H^+K^+-ATPase and it is also a substituent that gives orally active compounds. Replacing the 3-cyanomethyl with 3-hydroxymethyl decreased the antisecretory activity.

8,9-dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]pyrano[2,3-c]-pyridine-3-acetonitrile, i.e. a *tricyclic* imidazo[1,2-a]pyridine, is known from D4, D5 and US 4,468,400 (Schering Corporation). This compound had an antisecretory activity comparable to that of the compound "Sch 28080".

However, compounds having the cyanomethyl substituent have the disadvantage that cyanide is produced when the compound is metabolized, and such compounds is likely to be of limited clinical use. There is consequently a need for compounds which avoid a cyanomethyl substituent while retaining the antisecretory activity at an acceptable level.

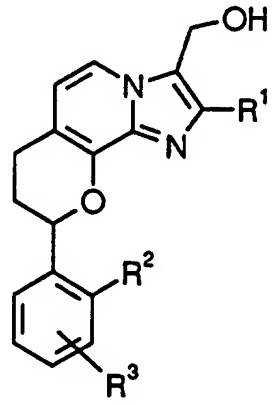
BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a scheme over Process A for preparation of compounds with the general Formula I.

DISCLOSURE OF THE INVENTION

Compounds of the Formula I, which are substituted tricyclic imidazo[1,2-a]pyridines, having a hydroxymethyl substituent in 3-position, are effective as inhibitors of gastric acid secretion, by reversibly inhibiting the gastrointestinal H^+,K^+-ATPase. It has surprisingly been found that the compounds according to the invention has improved properties concerning the farmacokinetics and metabolism. These properties together lead to an improved therapeutic profile.

In one aspect, the invention thus relates to compounds of the general Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) CH_3, or

(b) CH_2CH_3;

R^2 is

(a) H,

(b) halogen,

(c) lower alkyl,

(d) lower alkoxy, or

(e) OH;

R^3, which is in position 3, 4 ,5 or 6 of the phenyl ring, is

(a) H,

(b) halogen, or

(c) lower alkyl.

As used herein, the term "lower alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "lower alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

The term "halogen" includes fluoro, chloro, bromo and iodo.

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the present invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I.

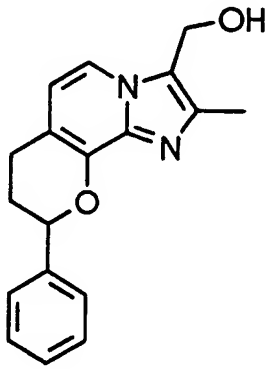
Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybensoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbensenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid.

Preferred compounds of the formula I are those wherein R^1 is CH_3 or CH_2CH_3; R^2 is H, CH_3, OH, OCH_3, OCH_2CH_3, F or Cl; and R^3 is H, 4-CH_3, 4-F or 4-Cl.

The most preferred compound of the invention is the compound wherein R^1 is CH_3; R^2 is H; and R^3 is H; i.e. the compound 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydropyrano[2,3-c]-imidazo[1,2-a]pyridine:



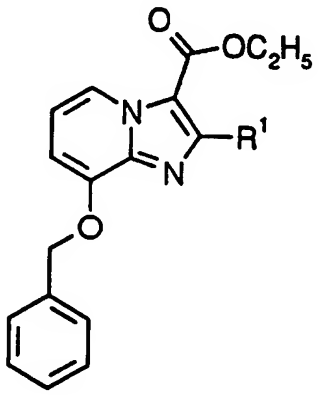
Preparation

The present invention also provides processes for the manufacture of compounds with the general Formula I.

Process A

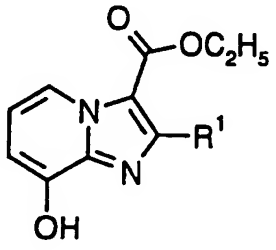
Process A for the manufacture of compounds with the general Formula I, with reference to the roman numbers in Fig. 1, comprises the following steps:

(a) Compounds of the general Formula VII can be prepared according to known methods described e.g. in Kaminski et al. (1985) J. Med. Chem. 28, 876-892.



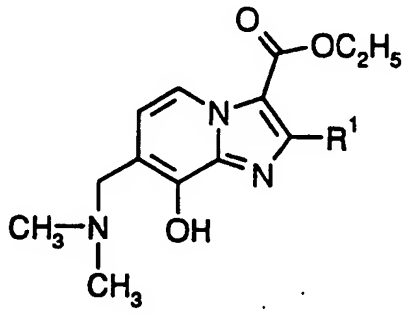
VII

Compounds of the general Formula VII, wherein R^1 is as defined for Formula I, can be debenzylated with e.g. cyclohexene in the presence of a catalyst (e.g. $Pd(OH)_2$) to the compound of the Formula VI wherein R^1 is as defined for Formula I. The reaction can be carried out under standard conditions e.g. by heating the reactants in an inert solvent, preferably ethanol.



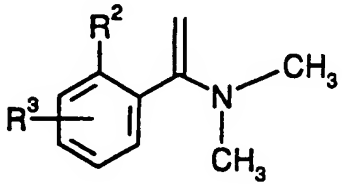
VI

(b) Compounds of the Formula V, wherein R^1 is as defined for Formula I, can be prepared by reacting compounds of the general Formula VI to a Mannich base with e.g. N,N-dimethylmethyleneammonium iodide in an inert solvent, e.g. methylene chloride, at ambient temperature.

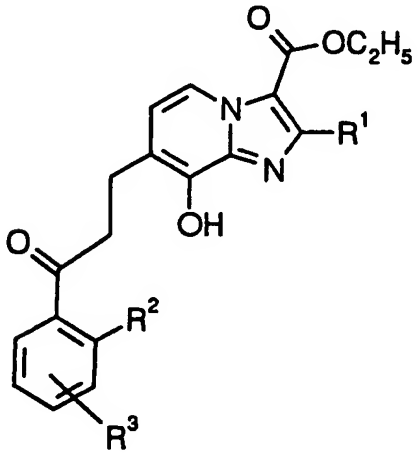


V

(c) Compounds of Formula V can be reacted with enamines of the general Formula VIII, wherein R^2 and R^3 are as defined for Formula I, to the compounds of the Formula IV, wherein R^1, R^2 and R^3 are as defined for Formula I. The reactions can be carried out according to methods described by von Standtmann, et al, J. Heterocyclic Chem. 7, 1311 (1970).

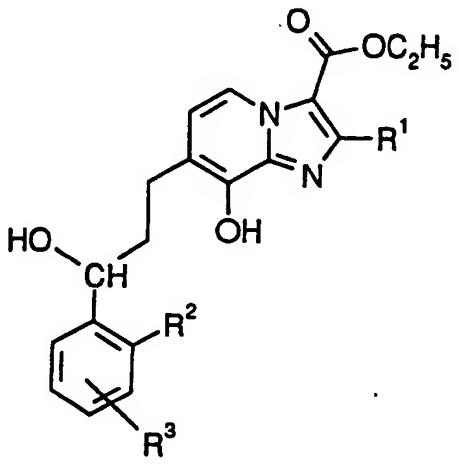


VIII



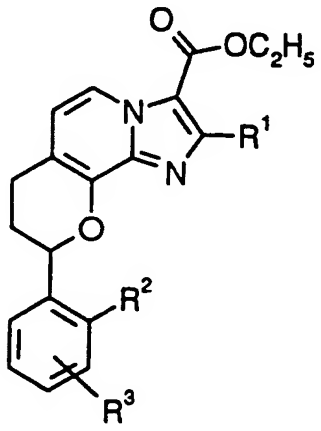
IV

(d) Compounds of Formula IV can be reduced (e.g. with $NaBH_4$) to the corresponding hydroxy compounds of Formula III, wherein R^1, R^2 and R^3 are as defined for Formula I. The solvent used for the reactions can e.g. be alcohols such as methanol and ethanol.



III

(e) The cyclizised compounds of Formula II, wherein R^1, R^2 and R^3 are as defined for Formula I, can be prepared by treating the compounds of Formula III with a Lewis acid (e.g. borontrifluoride etherate) under standard conditions in an inert solvent, e.g. methylene chloride.

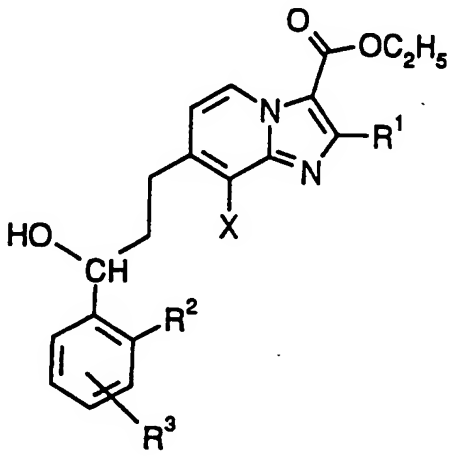


II

(f) Reduction of compounds of the general Formula II, e.g. by using lithium aluminium hydride in tetrahydrofuran or ether, yields the compounds of the general Formula I.

Process B

The phenolic hydroxy group in Formula III (see Process A) can be converted to a leaving group as for Formula IX, wherein R^1, R^2, and R^3 are as defined in Formula I and X is a leaving group e.g. mesylate, tosylate or triflate, by reacting the hydroxy group with such reagents as mesyl chloride, tosyl chloride or N-phenyltrifluoromethylsulfonimide. The reactions can be carried out under standard conditons with a base in an inert solvent, e.g methylene chloride or acetonitrile.



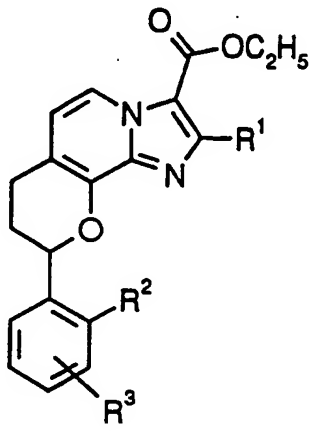
IX

The cyclizised compounds of Formula II (see Process A), wherein R^1, R^2, and R^3 are as defined for Formula I, can be prepared by treating the compounds of the Formula IX with a base e.g sodium hydride or potassium tert-butoxide in an inert solvent e.g. dimethylformamide or acetonitrile.

The alternative process B for the preparation of a compound according to the invention thus comprises:

(a) converting the phenolic hydroxygroup of a compound of the Formula III, wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula IX;

(b) ringclosure of a compound of the Formula IX, wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II; and

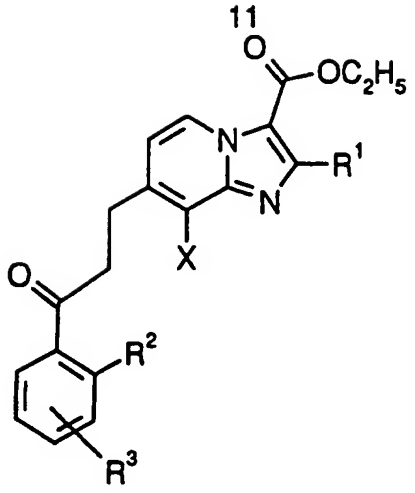


II

(c) reducing a compound of the Formula II, wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I.

Process C

The phenolic hydroxy group in Formula IV can be converted to a leaving group as for Formula X, wherein R^1, R^2, and R^3 are as defined in Formula I and X is a leaving group e.g. mesylate, tosylate or triflate, by reacting the hydroxy group with such reagents as mesyl chloride, tosyl chloride or N-phenyltrifluoromethylsulfonimide. The reactions can be carried out under standard conditons with a base in an inert solvent, e.g methylene chloride or acetonitrile.



X

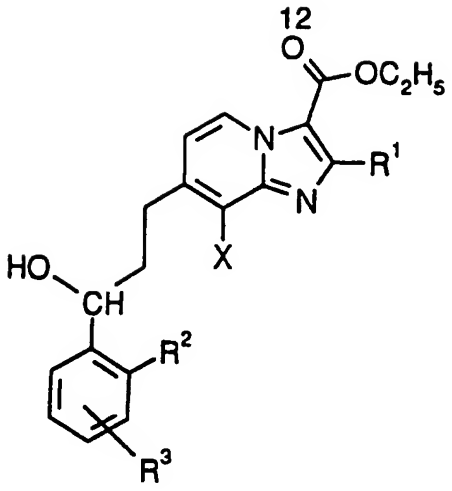
Compounds of the general Formula X can be reduced (e.g. with NaBH4) to the corresponding hydroxy compounds of Formula IX, wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group. The solvent used for the reactions are especially alcohols, e.g. methanol or ethanol.

The cyclizised compounds of Formula II (see Process A), wherein R^1, R^2, and R^3 are as defined for Formula I, can be prepared by treating the compounds of the Formula IX with a base e.g sodium hydride or potassium tert-butoxide in an inert solvent e.g. dimethyl formamide or acetonitrile.

The further alternative process C for the preparation of a compound according to the invention thus comprises:

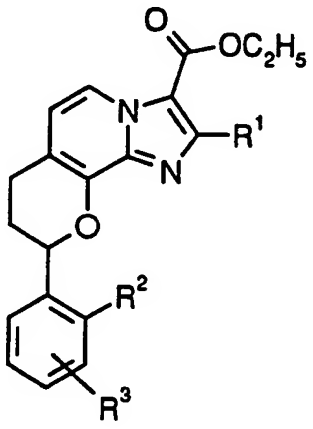
(a) converting the phenolic hydroxygroup of a compound of the Formula IV, wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula X;

(b) reducing a compound of the Formula X, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydroxy compound of the Formula IX;



IX

(c) ring closure of a compound of the Formula IX, wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II; and



II

(d) reducing a compound of the Formula II, wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I.

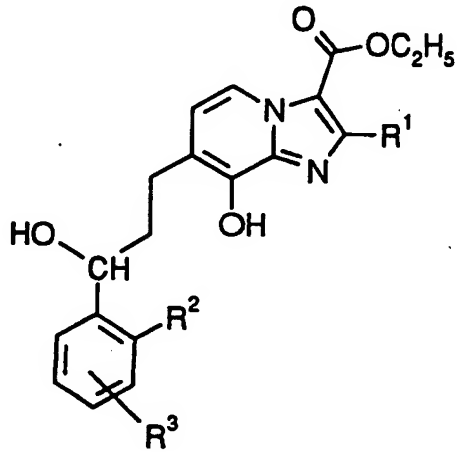
Preparation of enantiomers

The present invention also provides processes for the manufacture of the pure enantiomers of the compounds with the general Formula I.

Processes for the manufacture the pure enantiomers of compounds with the general Formula I, comprises the following steps:

Path A

Compounds of the general formula IV can be reduced with an enantioselective reduction with e.g. (+ or -)-DIP-chloride™ (Diisopinocampheyl chloroborane) to the corresponding hydroxy compounds of Formula III (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I. The solvent used for the reactions can e.g. be tetrahydrofuran or ether.



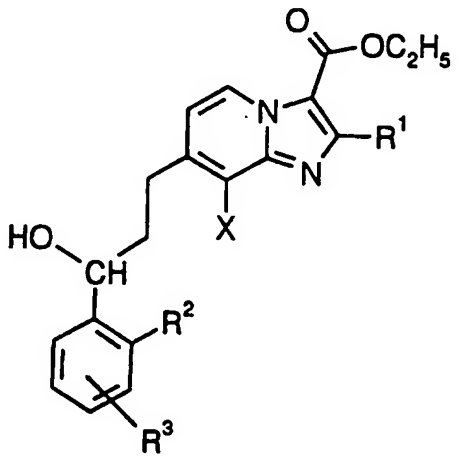
III (R or S)

Using Process B gives the pure enantiomers of compounds with the general Formula I.

A process for the preparation of the pure enantiomers of a compound according to the invention thus comprises:

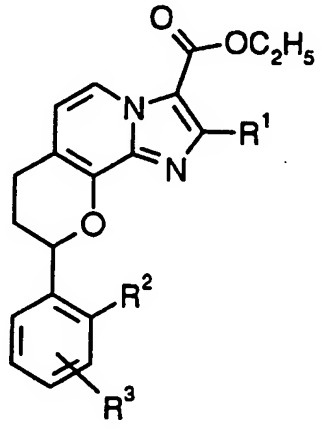
(a) enantioselective reduction of a compound of the Formula IV, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydroxygroup of a compound of the general Formula III (R or S);

(b) converting the phenolic hydroxygroup of a compound of the Formula III (R or S) wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula IX (R or S);



IX (R or S)

(c) ringclosure of a compound of the Formula IX (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II (R or S); and

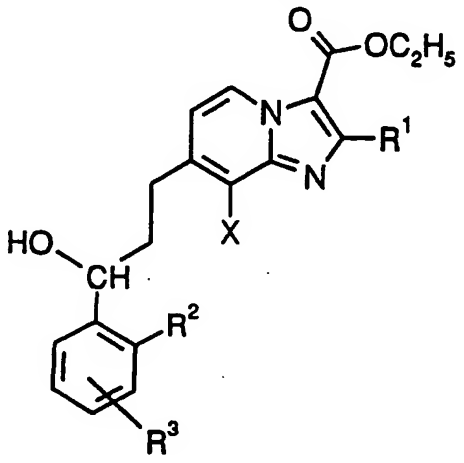


II (R or S)

(d) reducing a compound of the Formula II (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I (R or S).

Path B

Compounds of the general Formula X (see Process C) can be reduced with an enantio-selective reduction with e.g. (+ or -)-DIP-chloride™ (Diisopinocampheyl chloroborane) to the corresponding hydroxy compounds of Formula IX (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group. The solvent used for the reactions are especially tetrahydrofuran or ether.



IX (R or S)

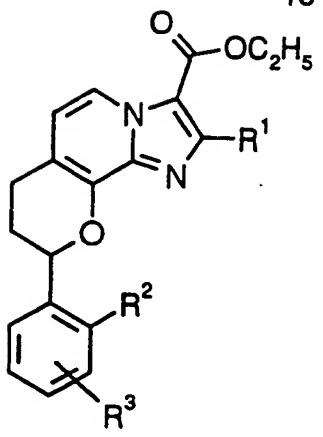
Using Process C gives the pure enantiomers of compounds with the general Formula I.

An alternative process for the preparation of the pure enantiomers of a compound according to the invention thus comprises:

(a) enantioselective reduction of a compound of the Formula X, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydroxy compound of the Formula IX (R or S);

(b) ringclosure of a compound of the Formula IX (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II (R or S); and

16



II (R or S)

(c) reducing a compound of the Formula II (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I (R or S).

Use

In a further aspect, the invention relates to the use of a compound as defined above for the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrom.

Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or

other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to by reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

EXAMPLES

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

3-Hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

To a solution of 4.2 g (12.4 mmol) of 8,9-dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester in 150 ml tetrahydrofuran there was added 1.8 g (47.5 mmol) lithium aluminium hydride in portions at ambient temperature under 3 h. To the reaction mixture was 1.8 ml water added dropwise followed by 1.8 ml 15% aqueous sodium hydroxide and then 5.4 ml water. The mixture was filtered in a sintered glass funnel and the filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with 2 M hydrochloric acid, and then basified to pH 8 with a bicarbonate solution. The methylene chloride layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual oil was chromatographed on silica gel, eluting with methylene chloride containing 10% methanol, crystallized from acetonitrile to obtain 2.5 g (68%) of the title compound.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 2.20-2.35 (m, 2H), 2.40 (s, 3H), 2.70-2.90 (m, 2H), 4.90 (s,2H), 5.20-5.30 (m,1H), 6.5 (d, 1H), 7.30-7.50 (m, 5H), 7.75 (d, 1H)

Example 1.2.

3-Hydroxymethyl-2-methyl-9-(4-fluorophenyl)-7H-8,9-dihydro-pyrano-[2,3-c]imidazo[1,2-a]pyridine

8,9-Dihydro-2-methyl-9-(4-fluorophenyl)-7H-imidazo[1,2-a]pyrano[2,3-c]-pyridine-3-carboxylic acid ethyl ester (1.0 g, 2.82 mmol) was dissolved in toluene (15 ml). The solution was cooled to 0 °C. 1.6 ml (5.9 mmol) of a 70% solution of sodium bis (2-methoxyethoxy) aluminum hydride in toluene was added. The mixture was stirred for 20 h at ambient temperature. An additional amount of 1 ml sodium bis (2-methoxyethoxy)aluminum was added and stirring was continued for 2 h at 50 °C. Water (3ml) was added carefully to the reaction mixture. The precipitate formed was filtered and washed with methylene chloride, acetone and methanol. The filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel, using methylene chloride containing 10 % methanol as eluent. 0.55 g (62 %) of the title compound was obtained.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 2.05-2.25 (m, 2H), 2.28 (s, 3H), 2.60-2.70 (m, 1H), 2.85-3.0 (m, 1H), 4.70 (s, 2H), 5,08 (broad s, 1H), 5.24 (dd, 1H), 6.63 (d, 1H), 7.22-7.29 (m, 2H), 7.49-7.55 (m, 2H), 7.85 (d, 1H).

2. PREPARATION OF INTERMEDIATES

Example 2.1

8-Hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

8-Benzyloxy-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (II) (95 g, 0.3 mol), ethanol (1000 ml), cyclohexan (600 ml), cyclohexene (200 ml)and palladium hydroxide (8 g) were mixed together and refluxed for 2 h. The catalyst was removed by filtration and the volatiles were removed under reduced pressure. Recrystallization from acetonitrile gave 45.5 g (69%) of the desired product.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.45 (t, 3H), 2.75 (s, 3H), 4.50 (q, 2H), 6.9-7.0 (m, 2H), 8.95 (dd, 1H)

Example 2.2

7-[(Dimethylamino)methyl]-8-hydroxy-2-methylimidazo-[1,2-a]pyridine-3-carboxylic acid ethyl ester

A mixture of 55 g (0.25 mol) of 8-hydroxy-2-methylimidazo- [1,2-a]pyridine-3-carboxylic acid ethyl ester and 50 g (0.26 mol) of N,N-dimethylmethylene-ammonium iodide in 1.75 l of methylene chloride was stirred at ambient temperature for 6 h. The reaction mixture was made basic by the addition of a sodium bicarbonate solution. The organic layer was separated and dried over anhydrous sodium sulfate. Drying agent was removed by filtration and the filtrate was evaporated under reduced pressure. The residual material was crystallized from ethyl acetate to obtain 40.7 g (59%) of the title compound.

(^{1}H-NMR, 500MHz, $CDCl_3$): 1.45 (t, 3H), 2.40 (s, 6H), 2.75 (s, 3H), 3.75 (s, 2H), 4.45 (q, 2H), 6.55 (d, 1H), 8.80 (d, 1H)

Example 2.3

7-(2-Benzoylethyl)-8-hydroxy-2-methylimidazo-[1,2-a]pyridine-3-carboxylic acid ethyl ester

7-[(dimethylamino)methyl]-8-hydroxy-2-methylimidazo[1,2-a] pyridine-3-carboxylic acid ethyl ester (1.0 g 3.61 mmol) was added to a stirred hot solution of 1-dimethylaminophenylethylene (1.2 g 8.18 mmol) in dry toluene (18 ml) under nitrogen. The reaction mixture was refluxed for 50 min. Vacuum evaporation of solvent gave an oily residue wich was subjected to flash chromatography on silica gel, methylene chloride : methanol (100:3), to give 1.45 g (85%) of the product as colorless crystals.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.45 (t, 3H), 2.70 (s, 3H), 3.25 (t, 2H), 3.45 (t, 2H), 4.45(q, 2H), 6.95 (d, 1H), 7.40-7.50 (m, 2H), 7.50-7.60 (m, 1H), 8.0 (d, 2H), 8.80 (d, 1H)

Example 2.4

8-Hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

A suspension of 5 g (12.9 mmol) of 7-(2-benzoylethyl)-8-hydroxy-2-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester hydrochloride in 150 ml ethanol and 50 ml of methylene chloride was treated with 1.6 g (42.3 mmol) of sodium borohydride added portionwise over 2 h. The volatiles were removed under reduced pressure and the residue was dissolved in methylene chloride, washed with 2 M hydrochloric acid was brought to pH 8

with a bicarbonate solution. The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure to obtain 4.4 g (96%) of the title compound as an oil.

(^{1}H-NMR, 500 MHz, DMSO-d_6): 1.40 (t, 3H), 1.80-1.90 (m, 2H), 2.6 (s, 3H), 2.60-2.75 (m, 2H), 4.40 (q, 2H), 4.50-4.60 (m, 1H), 6.9 (d, 1H), 7.20-7.40 (m, 5H), 8.70 (d, 1H)

Example 2.5

8,9-Dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]-pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester

To a solution of 4.4 g (12.4 mmol) of 8-hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)imidazo[1,2-a]pyridine in 150 ml of methylene chloride were added 4.4 ml (5 g, 35.6 mmol) of boron trifluoride etherate. After the mixture was stirred for 3 h at ambient temperature, another 1.5 ml (1.7 g, 12.1 mmol) of boron trifluoride etherate was added, and the mixture was stirred 3 h at ambient temperature. The reaction mixture was basified to pH 8 with a bicarbonate solution. The organic layer was separated dried over anhydrous sodium sulfate, and evaporated under reduced pressure to obtain 4.1 g (99%) of the desired compound.

(^{1}H-NMR, 500 MHz, DMSO-d_6): 1.45 (t, 3H), 1.25-1.35 (m, 2H), 1.70 (s, 3H), 1.70-3.0 (m, 2H), 4.40 (q, 2H) 5.25-5.35 (m, 1H), 6.65 (d,1H), 7.30-7.50 (m, 5H),8.85 (d,1H)

Example 2.6.

7-(2-(4-Fluorobenzoyl) ethyl)-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

7-[(Dimethylamino)methyl]-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (5.7 g, 20.6 mmol) was added to a stirred hot solution (100 °C) of 1-dimethylamino(4-fluorophenyl)ethylene (4.1 g, 25 mmol) in toluene (30 ml). The mixture was refluxed for 2 h and then cooled to room temperature. Water (5 ml) was added and the mixture was stirred for 16 h at ambient temperature. The mixture was then evaporated to dryness and the residue was triturated with methylene chloride (100 ml). Solid material was filtered off and the filtrate evaporated. The residue was refluxed in isopropanol (40 ml). After cooling the product was filtered and washed with isopropanol and aceton. 3.0 g (39%) of the title compound was obtained.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.39 (t, 3H), 2.61 (s, 3H), 3.21 (t, 2H), 3.40 (t, 2H), 4.36 (q, 2H), 6.94 (d, 1H), 7.09 (t, 2H), 7.98-8.04 (m, 2H), 8.80 (d, 1H).

Example 2.7.

8-Hydroxy-2-methyl-7-(3-(4-fluorophenyl)-3-hydroxypropyl)-imidazo[1,2-a]-pyridine-3-carboxylic acid ethyl ester

7-(2-(4-Fluorobenzoyl) ethyl)-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (3.0 g, 8.1 mmol) was dissolved in 25 ml ethanol. 370 mg (9.8 mmol) $NaBH_4$ was added portionwise over 1 h. The mixture was stirred at ambient temperature for 18 h. An additional amount of 350 mg $NaBH_4$ was added and the reaction was continued for 1 h at ambient temperature. Acetic acid (0.5 ml) was added. The reaction mixture was evaporated to dryness. The residue was extracted with methylene chloride and water. The organic layer was separated and evaporated. The residue was purified by column chromatography on silica gel. The product was

eluted with metylene chloride containing 8% methanol. 2.0 g (66%) of the title compound was obtained.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.39 (t, 3H), 1.95-2.05 (m, 2H), 2.56 (s, 3H), 2.80-
3.10 (m, 2H), 4.38 (q, 2H), 4.65-4.69 (m, 1H), 6.83 (d, 1H), 6.93-7.00 (m, 2H), 6.97 (t, 2H), 7.25-7.32 (m, 2H), 8.79 (d, 1H).

Example 2.8.

8,9-Dihydro-2-methyl-9-(4-fluorophenyl)-7H-imidazo[1,2-a]pyrano[2,3-c]-pyridine-3-carboxylic acid ethyl ester

8-Hydroxy-2-methyl-7-(3-(4-fluorophenyl)-3-hydroxypropyl)-imidazo[1,2-a]-pyridine-3-carboxylic acid ethyl ester (2.0 g, 5.37 mmol) was dissolved in methylene chloride (30 ml) and the solution cooled to -5 °C. 2 ml (2.26g, 15.9 mmol) boron trifluoride etherate was added and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was washed with sodium carbonate solution and the organic layer separated and evaporated to dryness. The residue was purified by column chromatography on silica gel. The product was eluted with a 70:30 mixture of methylene chloride and ethyl acetate. 1.0 g (53%) of the title compound was obtained.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.40 (t, 3H), 2.15-2.30 (m, 2H), 2.68 (s, 3H), 2.68-
2.80 (m, 1H), 2.90-3.0 (m, 1H), 4.38 (q, 2H), 5.25 (dd, 1H), 6.63 (d, 1H), 7.01 (t, 2H), 7.36-7.42 (m, 2H), 8.81 (d, 1H).

Preparation of racemate by process C

Example 2.9

7-(2-Benzoylethyl)-8-mesyl-2-methylimidazo-[1,2-a]pyridine-3-carboxylic acid ethyl ester

To a solution of 7-(2-Benzoylethyl)-8-hydroxy-2-methylimidazo-[1,2-a]pyridine-3-carboxylic acid ethyl ester (1.0 g 2.8 mmol) in methylene chloride (50 ml) was added 0.84 g (8.4 mmol) of triethyl amin and 0.93g (8.4 mmol) of mesyl chloride. After stirring the reaction mixture for 20 h water was added. The organic layer was separated dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The residue was triturated with diethyl ether, filtered and dried to give a powder of the titled product (0.9g, 83%).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 1.40 (t, 3H), 2.65 (s, 3H), 3.25 (t, 2H), 3.40 (t, 2H), 3.80 (s, 3H), 4.40 (q, 2H), 7.00 (d, 1H), 7.25 (t, 2H), 7.55 (t, 1H), 7.95 (d, 2H), 9.15 (d, 1H).

Example 2.10

8-Mesyl-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

To a solution of 7-(2-Benzoylethyl)-8-mesyl-2-methylimidazo-[1,2-a]pyridine-3-carboxylic acid ethyl ester (0.5g 1.2 mmol) in ethanol (20 ml) at 70 °C was added sodium hydride (0.05g 1.3 mmol) (55% in oil) and the mixture was stirred for 3 h at rom temperature. The mixture was concentrated under reduced pressure and the residue was dissolved in methylene chloride and washed with aqueous bicarbonate. The organic layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was triturated with diethyl ether to give a powder of the title product (0.25 g, 48%).

(^{1}H-NMR, 400 MHz, DMSO-d_6) : 1.40 (t, 3H), 2.10-2.20 (m, 2H), 2.65 (s, 3H), 2.90-3.00 (m, 2H), 3.80 (s, 3H), 4.40 (q, 2H), 4.47 (dd, 1H), 6.90 (d, 1H), 7.15-7.40 (m, 5H), 9.15 (d, 1H).

3. PREPARATION OF THE PURE ENANTIOMERS

3.1. Preparation by process B, path A

3.1.1. (-)Enantiomers

Example 3.1.1.1.

8-Hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

A solution of 1.0 g (2.8 mmol) 7-(2-benzoylethyl)-8-hydroxy-2-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester in tetrahydrofuran (10 ml) was cooled to -25 °C (argon atmosphere). (+)-Diisopinocampheyl-chloroborane (1.8 g, 5.6 mmol) was added and the mixture was stirred for 24 h. (temperature between -25°C and 0°C). Additional (+)-Diisopinocampheyl-chloroborane (1.1 g, 3.4 mmol) was added during a period of 7 h and the mixture was stirred for 15 h. The reaction mixture was allowed to reach R.T and methylene chloride 20 ml and aqueous sodium bicarbonate was added. The organic layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure to give an oily residue. The residue was twice subjected to flash chromatography on silica gel:metylene chloride : methanol a) 10:1 b) 100:5 , to give 0.55 g (55%) of the desired product as pure enatiomer.

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.4 (t, 3H), 2.0-2.25 (m, 2H), 2.65 (s, 3H), 2.75-2.85 (m, 1H), 2.95-3.10 (m, 1H), 4.0 (bs, 2H), 4.45 (q, 2H), 4.70 (dd, 1H), 6.85 (d, 1H), 7.20-7.40 (m, 5H), 8.85 (d, 1H).

Example 3.1.1.2

8-Mesyl-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

To a solution of 8-hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (0.5 g 1.4 mmol) in acetonitril (25 ml) was added 0.32 g (2.0 mmol) of potassium carbonate and 0.16 ml (2.0 mmol) of mesyl chloride. The reaction mixture was stirred for 16 h, filtred and the filtrate was evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel, methylene chloride : methanol (100:5), to give the pure enantiomer of the title compound 0.4 g (66%).

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.45 (t, 3H), 2.05-2.15 (m, 2H), 2.65 (s, 3H), 2.95-3.05 (m, 2H), 3.80 (s, 3H), 4.45 (q, 2H), 4.70-4.80 (m, 1H), 6.90 (d, 1H), 7.20-7.40 (m, 5H), 9.10 (d, 1H).

Example 3.1.1.3

8,9-Dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]-pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester

Sodium hydride (0.04 g 0.93 mmol)(55% in oil) was added to a solution of 8-mesyl-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (0.4 g 0.93 mmol) in dimethylformamide (15 ml) at 5 °C. The reaction mixture was stirred for 3 h. at 5 °C and 30 min. at

ambient temperature and was then concentrated under reduced pressure. The residue was dissolved in methylene chloride washed with aqueous bicarbonate. The organic layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified twice by column chromatography on silica gel with a mixture of dichloromethane and methanol (100:1 and 100:5) as eluent to give the pure enantiomer (96.6 % ee) of the title product as an oil. (0.18 g 58%)

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.40 (t, 3H), 2.10-2.35 (m, 2H), 2.60-2.75 (m, 4H), 2.80-2.95 (m, 1H), 4.40 (q, 2H), 5.25 (dd, 1H), 6.60 (d, 1H), 7.20-7.40 (m, 5H), 8.80 (d, 1H).

Example 3.1.1.4

(-)-3-Hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

To a solution of 0.17g (0.51 mmol) of the pure enantiomer 8,9-dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]-pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester in toluen (10 ml) was added 0.6 ml (2.1 mmol) of sodium bis (2-methoxyethoxy) aluminium hydride and the reaction mixture was stirred for 3 h at ambient temperature. The reaction was stopped by adding 0.3 ml water and the reaction mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride, washed with water and dried over sodium sulfate. The solvent was evaporated under reduced pressure and was triturated with a mixture of acetonitril and ether(50:50) affording powder of the pure enantiomer (96% ee) of the title product. (0.05g 33%)

(^{1}H-NMR, 300 MHz, $CDCl_3$): 2.05-2.40 (m, 5H), 2.65-2.75 (m, 1H), 2.85-3.00 (m, 1H), 4.85 (s, 2H), 5.25 (dd, 1H), 6.50 (d, 1H), 7.25-7.50 (m, 5H), 7.80 (d, 1H).

3.1.2. (+)-Enantiomers

Example 3.1.2.1

8-Hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

A solution of 14.0 g (40.0 mmol) 7-(2-benzoylethyl)-8-hydroxy-2-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester in tetrahydrofuran (400 ml) was cooled to -50 °C (argon atmosphere). (-)-Diisopinocampheyl-chloroborane (50 g, 155 mmol) and the mixture was stirred for 24 h. (temperature between -25°C and -5°C). To the reaction mixture was added acetaldehyd (12.3g 280 mmol) and the mixture was allowed to reach R.T and was stirred for 1.5 h. To the mixture (after cooling to 5 °C) was added ether (200 ml) and 2M NaOH (200 ml) and was stirred for 20 min. at the same temperature. The organic layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure. The oily product was dissolved in ether and was converted to hydrochloride salt by adding a HCL-ether solution and the resultant precipitate was filtered off. The salt was dissolved in methylene chloride and was basified with 2M NaOH. The organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a residue, which was triturated in petrol ether to give a powder of the pure enantiomer of the title compound.(10.7g 76%)

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.45 (t, 3H), 2.00-2.25 (m, 2H), 2.65 (s, 3H), 2.80-2.90 (m, 1H), 3.00-3.15 (m, 1H), 4.40 (q, 2H), 4.70 (m, 1H), 6.90 (d, 1H), 7.20-7.40 (m, 5H), 8.85 (d, 1H).

Example 3.1.2.2

8-Mesyl-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

To a solution of 8-Hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (10.0g 28 mmol) in acetonitril (200 ml) was added 7.7g (55 mmol) of potassium carbonate and 4.8g (38 mmol) of mesyl chloride. The reaction mixture was stirred for 24 h, filtred and thesolvent was evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel, methylene chloride : methanol (100:5), to give the pure enantiomer of the title compound 8.0g (66%).

(^{1}H-NMR, 400 MHz, $CDCl_3$): 1.40 (t, 3H), 2.05-2.10 (m, 2H), 2.70 (s, 3H), 2.95-3.00 (m, 2H), 3.75 (s, 3H), 4.40 (q, 2H), 4.85-4.90 (m, 1H), 6.85 (d, 1H), 7.15-7.40 (m, 5H), 9.10 (d, 1H).

Example 3.1.2.3

8,9-Dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]-pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester

Sodium hydride (1.0 g 22.5 mmol) (55% in oil) was added to a solution of 8-mesyl-2-methyl-7-(3-phenyl-3-hydroxypropyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (7.8 g 18.0 mmol) in dimethylformamide 100 ml at 5 °C. The reaction mixture was stirred for 6 h. at ambient temperature and

was then concentrated under reduced pressure. The residue was dissolved in methylene chloride washed with aqueous bicarbonate. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate:petroleum ether (50:50) as eluent to give the pure enantiomer (90% ee) of the title product as an oil. (3.37g 62%)

(^{1}H-NMR, 300 MHz, $CDCl_3$): 1.45 (t, 3H), 2.20-2.40 (m, 2H), 2.70-2.85 (m, 4H), 2.90-3.00 (m, 1H), 4.40 (q, 2H), 5.35 (dd, 1H), 6.70 (d, 1H), 7.30-7.50 (m, 5H), 8.80 (d, 1H).

Example 3.1.2.4

(+)-3-Hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

To a solution of 3.7 g (0.11mmol) of the pure enantiomer 8,9-dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]-pyrano[2,3-c]pyridine-3-carboxylic acid ethyl ester in 40 ml toluen was added slowly 9.0 ml (33.0 mmol) of sodium bis (2-methoxyethoxy) aluminium hydride in 15 ml toluen for 2 h at 5 °C and the reaction mixture was stirred for 5 h. at ambient temperature. The reaction was cooled to 5 °C and was stopped by adding 7.0 ml water slowly and the reaction mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was purified by column chromathography on silica gel with a mixture of dichloromethane and methanol (10:1) as an eluent to give a powder of the pure enantiomer (90.2% ee) of the title product. (2.7g 90%)

(^{1}H-NMR, 300 MHz, $CDCl_3$): 2.15-2.35 (m, 2H), 2.40 (s, 3H), 2.65-2.75 (m, 1H), 2.85-2.95 (m, 1H) 4.90 (s, 2H), 5.30 (dd, 1H), 6.55 (d, 1H), 7.25-7.50 (m, 5H), 7.80 (d, 1H).

Example 3.3.

Resolution of the compound according to Example 1.1

(a) A hot solution of 0.52 g (1.7mmol) [(1R)-(endo,anti)]-(+)-3-bromocamphor-8-sulfonic acid and 0.5 g (1.7mmol) of racemic 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydropyrano[2,3-c]imidazo-[1,2-a]pyridine in 11 ml ethanol was allowed to cool to room temperature and was stirred for 24 h. The crystalline salt filtered off (the filtrate was used in (b)). The recrystallization was repeated four times, finally yielding 9 mg of the salt. The salt was solved in methylene chloride and basified with a sodium bicarbonate solution. The organic layer was separated dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 3.9 mg of the enantiomer as an oil.

(b) The filtrate from the first crystallisation in (a) was evaporated under reduced pressure. The residue was solved in methylene chloride and was made basic by the addition of a sodium bicarbonate solution.The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure, yielding 150 mg of an oil. This oil (150 mg, 0.5 mmol) was solved in 2.5 ml hot ethanol and to the solution was added 0.16 g (0.5 mmol) of [(1S)-(endo,anti)]-(-)-3-bromocamphor-8-sulfonic acid. The solution was allowed to cool to room temperature and was stirred for 24 h. The crystalline material was filtered off. This recrystallization was repeated twice. Working up as in (a) gave 6.9 mg of the enantiomer as an oil.

The enantiomers was separated on a 250 X 4.6 mm i.d. Chiralpak AD column (Daciel,Japan) using the following parameters: mobilphase: n-hexane : 2-

propanol : acetonitrile : diethyl amin (84:16:2.5:0.1 ml); temperature: 35°C; flow rate: 0.8 ml/min.

Enantiomer according to (a): retention time 12.0 min

Enantiomer according to (b): retention time 13.6 min

4. PREPARATION OF SALTS

Example 4.1.

Preparation of the hydrochloride salt of 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (0.5g, 1.7 mmol) was dissolved in hot ethanol (10 ml) and was cooled to room temperature. A solution of hydrogen chloride in diethyl ether (4 ml) was added and the reaction mixture was stirred for 10 min. The resulting white solid was filtered off and dried to give the title salt. (0.35g, 62%)

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.15-2.25 (m, 1H), 2.30-2.40 (m, 1H) 2.50 (s, 3H), 2.85-2.95 (m, 1H), 3.05-3.15 (m, 1H),4.85 (s,2H), 5.45-5.55 (m,1H),5.75 (bs, 1H), 7.35 (d, 1H), 7.40-7.60 (m, 5H), 8.35 (d, 1H) .

Example 4.2.

Preparation of the methanesulfonic acid salt of 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (0.5g, 1.7 mmol) was dissolved in hot ethanol (5 ml). To the solution was added methanesulfonic acid (0.11 ml, 1.7 mmol) and the mixture was stirred for 15 min at room temperature. The resulting white solid was filtered off and dried to give the title salt (0.5g, 75%).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.10-2.20 (m, 1H), 2.30 (s, 3H) 2.35-2.2.55 (m, 4H), 2.85-2.95 (m, 1H), 3.05-3.15 (m,1H), 4.85 (s,2H), 5.40-5.50 (m,1H), 7.30 (d, 1H), 7.35-7.65 (m, 5H), 8.30 (d, 1H) .

Example 4.3.

Preparation of the hydrogen sulfate salt of 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (0.5g, 1.7 mmol) was dissolved in hot ethanol (5 ml). To the solution was added sulfuric acid (95ml, 1.7 mmol) and the mixture was stirred for 15 min at room temperature. The resulting white solid was filtered off and dried to give the title salt (0.5g, 75%).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.15-2.25 (m, 1H), 2.30-2.40 (m, 1H) 2.45 (s, 3H), 2.85-2.95 (m, 1H), 3.10-3.20 (m, 1H),4.85 (s,2H), 5.45-5.55 (m,1H), 7.35 (d, 1H), 7.40-7.60 (m, 5H), 8.30 (d, 1H) .

Example 4.4.

Preparation of di-[3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine] tartaric acid salt

3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (1.0 g, 3.4 mmol) was dissolved in a mixture of diethyl ether (4 ml) and ethanol (5 ml). To the solution was added tartaric acid (0.5g, 3.4 mmol) dissolved in hot ethanol (3 ml). The mixture was stirred at room temperature over night. The resulting white solid was filtered off and dried to give the title salt (0.8g, 64%).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.05-2.15 (m, 2H), 2.20-2.40 (m, 8H) 2.60-2.75 (m, 2H), 2.90-3.00 (m, 2H), 4.25 (s, 2H),4.70 (s,4H), 5.20-5.30 (m,2H), 6.7 (d, 2H), 7.30-7.55 (m, 10H), 7.90 (d, 2H) .

Example 4.5.

Preparation of the methanesulfonic acid salt of (+)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

(+)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (4.7 g, 16.0 mmol) was dissolved in a hot mixture of ethyl acetate (60 ml) and ethanol (22 ml). To the solution was added methanesulfonic acid (1.6 g , 16.7 mmol) solved in 3 ml ethyl acetate and the mixture was stirred for 15 min at room temperature. An additional amount of ethyl acetate was added (15 ml) and the resulting white solid was filtered off and dried to give the title salt (5.7 g, 91%) (91.2% ee).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.10-2.25 (m, 1 H), 2.30 (s, 3H), 2.35-2.45 (m, 4H), 2.85-2.95 (m, 1H), 3.05-3.20 (m, 1H), 4.85 (s, 2H), 5.50 (dd, 1H), 5.60 (bs, 1H), 7.35 (d, 1H), 7.40-7.65 (m, 5H), 8.35 (d, 1H).

Example 4.6.

Preparation of the methanesulfonic acid salt of (-)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine

(-)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]-imidazo[1,2-a]pyridine (4.0 g, 13.6 mmol) was dissolved in a hot mixture of ethyl acetate (30 ml) and ethanol (12 ml). To the solution was added methanesulfonic acid (1.4 g, 15.0 mmol) solved in 2 ml ethyl acetate and the mixture was stirred for 15 min at room temperature. An additional amount of ethyl acetate was added (15 ml) and the resulting white solid was filtered off and dried to give the title salt (5.0 g, 94%) (92% ee).

(^{1}H-NMR, 300 MHz, DMSO-d_6) : 2.10-2.25 (m, 1 H), 2.30 (s, 3H), 2.35-2.45 (m, 4H), 2.85-2.95 (m, 1H), 3.05-3.20 (m, 1H), 4.85 (s, 2H), 5.50 (dd, 1H), 5.60 (bs, 1H), 7.35 (d, 1H), 7.40-7.65 (m, 5H), 8.35 (d, 1H).

5. PREPARATION OF PHARMACEUTICAL FORMULATIONS

Pharmaceutical formulations containing a compound of the invention as active ingredient are illustrated in the following examples:

Example 5.1: Syrup

A syrup containing 1% (weight per volume) of active substance is prepared from the following ingredients:

Acid addition salt of the compound according to Example 1.1	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g

Glycerol	5.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine are dissolved in 60 g of warm water. After cooling the acid addition salt is dissolved in the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol are added. The mixture is diluted with water to a final volume of 100 ml.

Example 5.2: Tablets

A tablet containing 50 mg of active compound is prepared from the following ingredients:

I	Compound according to Example 1.1	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Hydroxypropyl methylcellulose	36 g
	Polyethylene glycol	9 g
	Colour Titanium dioxide	4 g
	Purified water	313 g

I. Compound according to Example 1.1, powder, is mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet is forced through a sieve and the granulate dried in an oven. After drying, the granulate is mixed with polyvinylpyrrolidone and magnesium

stearate. The dry mixture is pressed into tablet cores (10,000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II. A solution of hydroxypropyl methylcellulose and polyethylene glycol in purified water is prepared. After dispersion of titanium dioxide the solution is sprayed onto the tablets I in an Accela Cota®, Manesty coating equipment. A final tablet weight of 130 mg is obtained.

Example 5.3: Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, is prepared from the following ingredients:

Compound according to Example 1.1	4 g
Polyethylene glycol 400 for injection	400 g
Disodium hydrogen phosphate	q.s.
Sterile water to a final colume of	1.000 ml

Compound according to Example 1.1 is dissolved in polyethylene glycol 400 and 550 ml of water is added. The pH of the solution is brought to pH 7.4 by adding a water solution of disodium hydrogen phosphate and water is added to a final volume of 1000 ml. The solution is filtered through a 0.22 µm filter and immediately despensed into 10 ml sterile ampoules. The ampoules are sealed.

6. BIOLOGICAL TESTS

6.1. Acid secretion inhibition in isolated rabbit gastric glands

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414. The compound according to Example 1.1 of the invention had an IC_{50} value of 0.25 μM.

Bioavailability

Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

Potency for inhibition of acid secretion

The potency for inhibition of acid secretion is measured in the rat intraduodenally and intravenously, and orally in the dog.

6.2. Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawly strain were used. They were equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A fourteen days recovery period after surgery was allowed before testing commenced.

Before secretory tests, the animals were deprived of food but not water for 20 h. The stomach was repeatedly washed through the gastric cannula with tap water (37°C), and 6 ml of Ringer-Glucose given subcutaneously. Acid secretion was stimulated with infusion during 3 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions were collected in 30-min

fractions. Test substances or vehicles were given intravenously or intraduodenally at 60 min after starting the stimulation, in a volume of 1.2 ml/h. Gastric juice samples were titrated to pH 7.0 with NaOH, 0.1 mol/l, and acid output calculated as the product of titrant volume and concentration.

Further calculations were based on group mean responses from 4-5 rats. The acid output during the periods after administration of test substances or vehicle were expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition was calculated from the fractional responses elicited by test compound and vehicle. ED_{50} values were obtained from graphical interpolation on log dose-response curves, or estimated form single-dose experiments assuming a similar slope for all dose-response curves.

The compound according to Example 1.1 of the invention had after id administration an ED_{50} value of 1.8 µmol/kg. The result are based on gastric acid secretion during the period from 30 to 60 minutes after drug/vehicle administration.

6.3. Bioavailability in rat

Adult rats of the Sprague-Dawley strain were used. One to three days prior to the experiments all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments were also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol. 15, 727-728). The cannulas were exteriorized at the nape of the neck. The compound according to Example 1.1 was given intraduodenally (10 µmol/kg) or intravenously (5 µmol/kg) as a bolus for about 0.5 min (2 ml/kg). 12 µmol/kg of the compound according to Example 1.1 was given orally by gavage and the dose 4 µmol/kg was given intravenously as a bolus for about

0.5 min (2 ml/kg). For compound A for comparison, the dose 40 µmol/kg was given orally by gavage and the dose 45 µmol/kg was given intravenously as a bolus.

Blood samples (0.1 - 0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen until analysis o f the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal administration was calculated as

F(%) = (AUC (p.o. or i.d.) / AUC (i.v.)) x 100.

6.4. Inhibition of gastric acid secretion and bioavailability in the concious dog.

Labrador retreiver or Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhain-pouch for the collection of gastric secretion.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated for up to 4 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. test substance or vehicle was given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is adminstered to the acid secreting main stomach of the Heidenham-pouch dog.

The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50}-values were obtained by graphical interpolation on log dose - response curves, or estimated under the assumption of the same slope of the dose-response curve for all test compounds. All results are based on acid output during the period from 1.5 to 2 hours after dosing.

Blood samples for the analysis of test compound concentration in plasma were taken at intervals up to 4 h after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral i.d. administration was calculated as described above in the rat model.

6.5. Determination of cyanide

The cyanide in whole blood was determinated as described by Lundquist et al. (1985) Clin. Chem. vol 31. No. 4., p. 591-595. Administration of 8 µmol/kg i.d. of compound B for comparison repeated once daily for 8 days was done in four dogs. Cyanide concentration was determinated in whole blood day 1, day 4 and day 8. The result is given as medium cyanide peak concentration in whole blood 5-15 minutes (Tmax) after the dose and the min and max value of the cyanide peak concentration determined in whole blood from four dogs.

The compounds for comparison in Table 1 are:

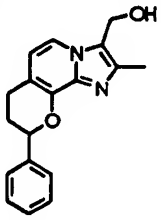
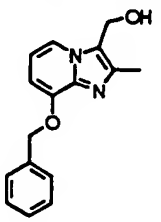
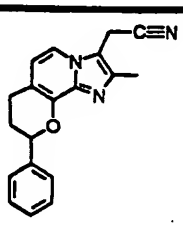
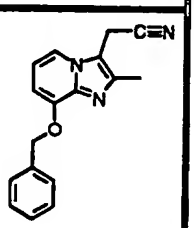
A: (3-(hydroxymethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine);

B: (8,9-dihydro-2-methyl-9-phenyl-7H-imidazo[1,2-a]pyrano[2,3-c]-pyridine-3-acetonitrile); and

C : (3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine).

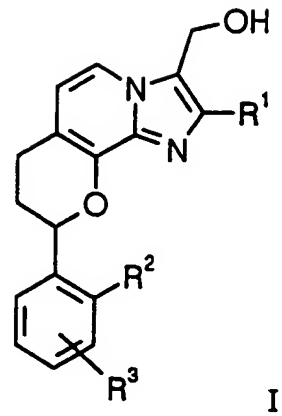
TABLE 1

Summary of the biological tests.

	Compound according to Example 1.1	Examples for comparison		
		A	B	C
				
6.1. Gastric glands IC_{50} (µM)	0.25	0.43	0.064 Value from D5	0.065 Value from D5
6.2.(a) Rat i.v. ED_{50} (µmol/kg)	1	1		
6.2. (b) Rat i.d. ED_{50} (µmol/kg)	1.8	6.4		
6.3. Rat - bioavailability (%)	54 (i.d.) 23 (p.o.)	12 (p.o.)		
6.4.(a) Dog p.o. ED_{50} (µmol/kg)	16	29.8 Value from D1	12.2 Value from D4	15.9 Value from D1
6.4.(b) Dog - bioavailability i.d. (%)	18	2.3 (Beagles)		
6.5.(a) CN^- peak concentration in dog, whole blood (µM)	-	-	3.3	
6.5.(b) CN^- in dog measured as SCN^- in urine (%)	-	-		20.2 Value from D2

CLAIMS

1. A compound of the Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) CH_3, or

(b) CH_2CH_3;

R^2 is

(a) H,

(b) halogen,

(c) lower alkyl,

(d) lower alkoxy, or

(e) OH;

R^3, which is in position 3, 4 ,5 or 6 of the phenyl ring, is

(a) H,

(b) halogen, or

(c) lower alkyl.

2. A compound according to claim 1 wherein R^1 is CH_3 or CH_2CH_3; R^2 is H, CH_3, OH, OCH_3, OCH_2CH_3, F or Cl; and R^3 is H, 4-CH_3, 4-F or 4-Cl, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 wherein R^1 is CH_3, R^2 is H and R^3 is H, i.e. the compound 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydropyrano[2,3-c]-imidazo[1,2-a]pyridine, or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 2 wherein R^1 is CH_3, R^2 is H and R^3 is 4-F, i.e. the compound 3-hydroxymethyl-2-methyl-9-(4-fluorophenyl)-7H-8,9-dihydropyrano[2,3-c]imidazo[1,2-a]pyridine or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 3 which is the compound (+)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydropyrano[2,3-c]-imidazo[1,2-a]pyridine or a pharmaceutically acceptable salt thereof.

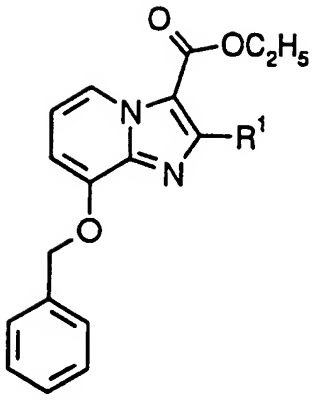
6. A compound according to claim 3 which is the compound (–)-3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydropyrano[2,3-c]-imidazo[1,2-a]pyridine or a pharmaceutically acceptable salt thereof.

7. A compound which is a hydrochloride salt of a compound according to any one of claims 1 to 6.

8. A compound which is a methanesulfonic acid salt of a compound according to any one of claims 1 to 6.

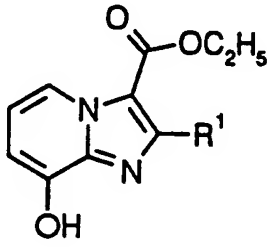
9. A process for the preparation of a compound according to any one of claims 1 to 8 comprising

(a) debenzylating a compound of the Formula VII



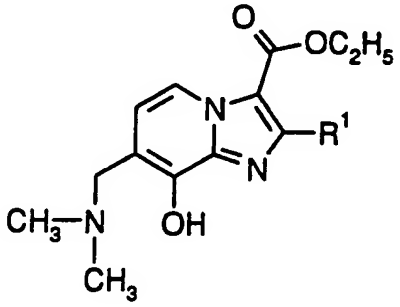
VII

wherein R^1 is as defined for Formula I, in the presence of a catalyst, to the compound of the Formula VI;



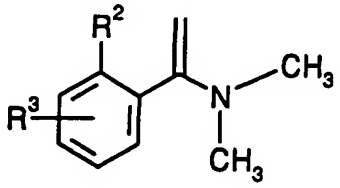
VI

(b) reacting a compound of the general Formula VI, wherein R^1 is as defined for Formula I, in a Mannich reaction in an inert solvent, to prepare a compound of the Formula V;



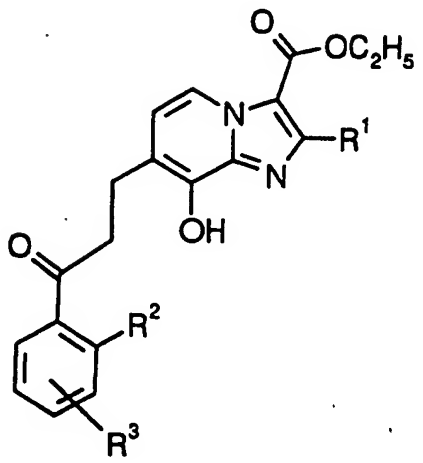
V

(c) reacting a compound of Formula V, wherein R^1 is as defined for Formula I, with an enamine of the general Formula VIII



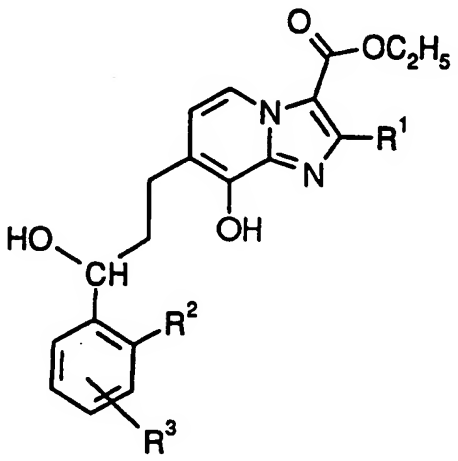
VIII

wherein R^2 and R^3 are as defined for Formula I, to a compound of the Formula IV;



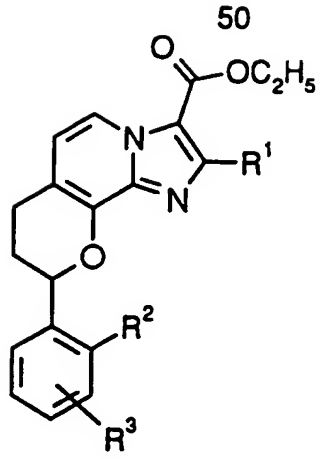
IV

(d) reducing a compound of Formula IV, wherein R^1, R^2 and R^3 are as defined for Formula I, to the corresponding hydroxy compound of Formula III;



III

(e) treating a compound of Formula III, wherein R^1, R^2 and R^3 are as defined for Formula I, with a Lewis acid under standard conditions in an inert solvent, thereby forming a compound of Formula II; and

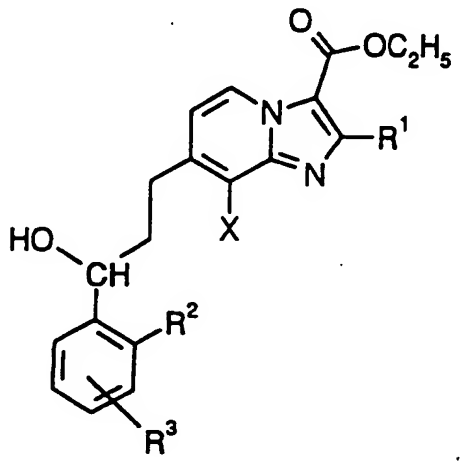


II

(f) reducing a compound of the Formula II, wherein R^1, R^2 and R^3 are as defined for Formula I, to a compound of the general Formula I.

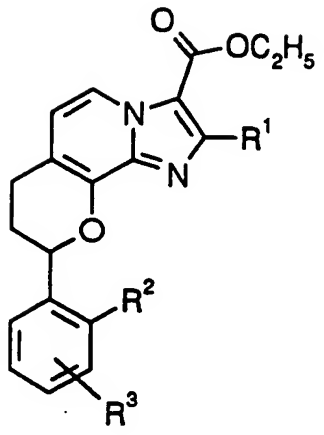
10. A process for the preparation of a compound according to any one of claims 1 to 8 comprising

(a) converting the phenolic hydroxygroup of a compound of the Formula III, wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula IX;



IX

(b) ringclosure of a compound of the Formula IX, wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II; and

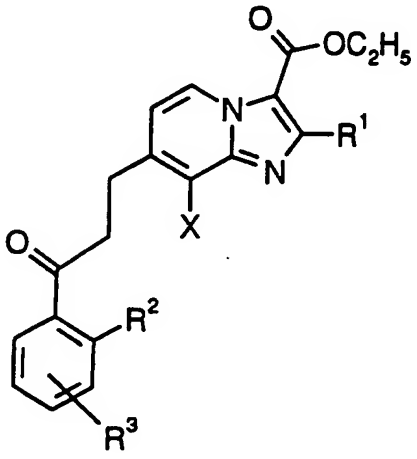


II

(c) reducing a compound of the Formula II, wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I.

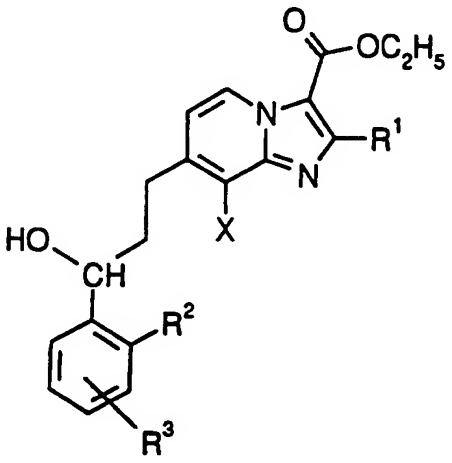
11. A process for the preparation of a compound according to any one of claims 1 to 8 comprising

(a) converting the phenolic hydroxygroup of a compound of the Formula IV, wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula X;



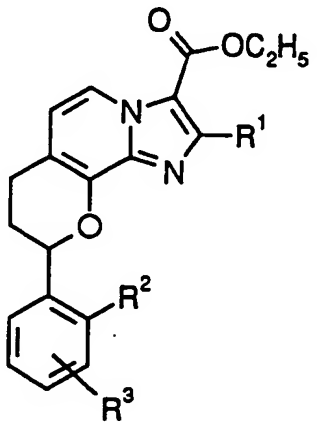
X

(b) reducing a compound of the Formula X, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydroxy compound of the Formula IX;



IX

(c) ringclosure of a compound of the Formula IX, wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II; and

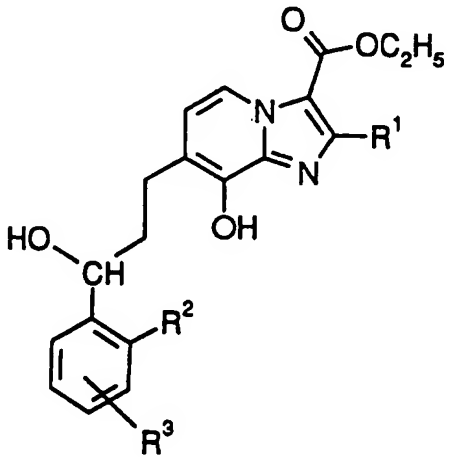


II

(d) reducing a compound of the Formula II, wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I.

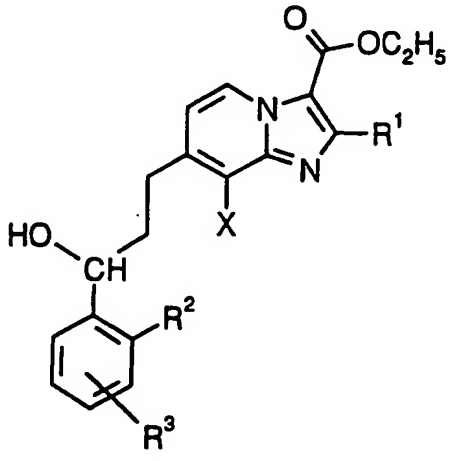
12. A process for the preparation of the pure enantiomers of a compound according to any one of claims 1 to 8 comprising

(a) enantioselective reduction of a compound of the Formula IV, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydoxygroup of a compound of the general Formula III (R or S);



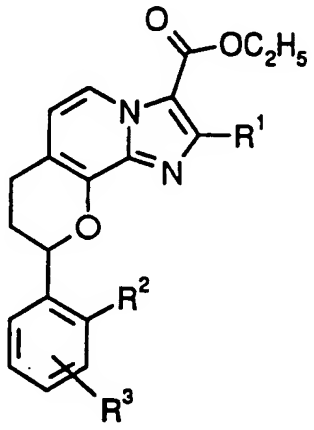
III (R or S)

(b) converting the phenolic hydroxygroup of a compound of the Formula III (R or S) wherein R^1, R^2, and R^3 are as defined for Formula I, to a leaving group X resulting in a compound of the general Formula IX (R or S);



IX (R or S)

(c) ringclosure of a compound of the Formula IX (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II (R or S); and

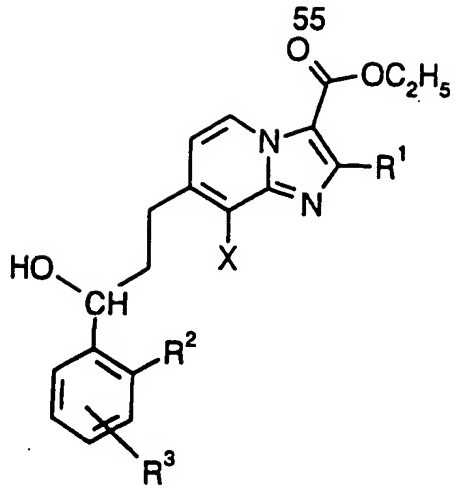


II (R or S)

(d) reducing a compound of the Formula II (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I (R or S).

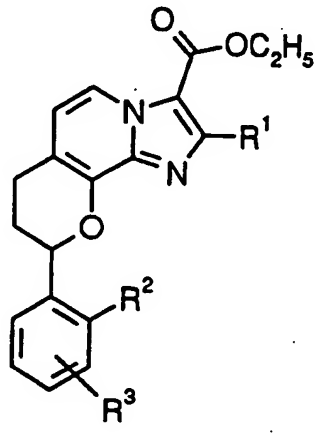
13. A process for the preparation of the pure enantiomers of a compound according to any one of claims 1 to 8 comprising

(a) enantioselective reduction of a compound of the Formula X, wherein R^1, R^2, and R^3 are as defined for Formula I, to the corresponding hydroxy compound of the Formula IX (R or S);



IX (R or S)

(b) ringclosure of a compound of the Formula IX (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I and X is a leaving group, with a base in an inert solvent, to a compound of the general Formula II (R or S); and



II (R or S)

(c) reducing a compound of the Formula II (R or S), wherein R^1, R^2, and R^3 are as defined for Formula I, to a compound of the Formula I (R or S).

14. A compound according to any one of claims 1 to 8 for use in therapy.

15. A pharmaceutical formulation containing a compound according to any one of claims 1 to 8 as active ingredient and comprising a pharmaceutically acceptable carrier.

16. Use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the inhibition of gastric acid secretion.

17. Use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.

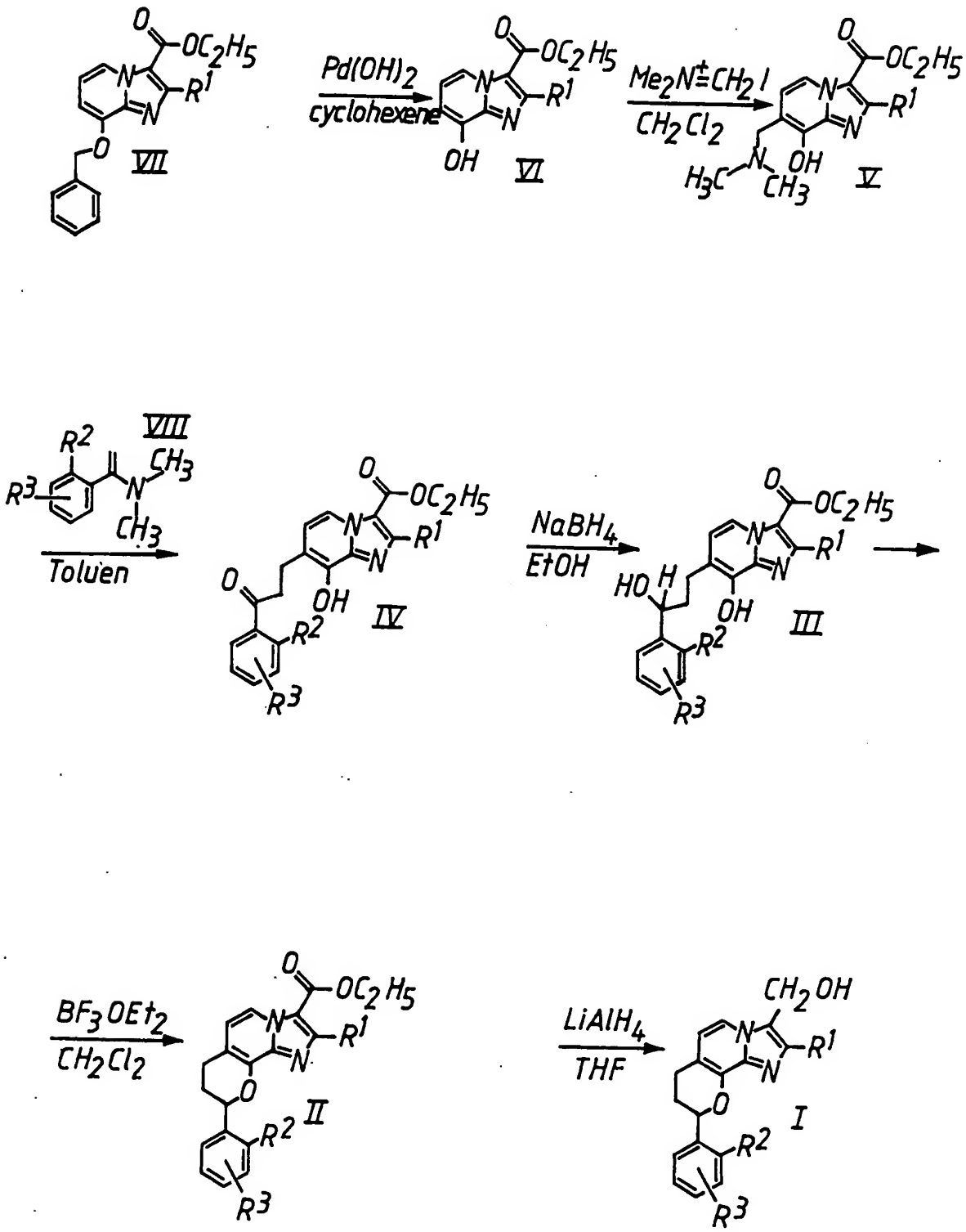
18. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 8.

19. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 8.

20. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 8.

21. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 8.

Fig. 1


Pd(OH)2
cyclohexene
Me2N≡CH2 I
CH2Cl2
VII
VI
V
VIII
Toluen
IV
NaBH4
EtOH
III
BF3OEt2
CH2Cl2
II
LiAlH4
THF
I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00376

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 491/052, A61K 31/415, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4468400 A (E. H. GOLD ET AL), 28 August 1984 (28.08.84) --	1-17,20-21
X	J. Med. Chem., Volume 34, 1991, J.J. Kaminski et al, "Antiulcer Agents. 5. Inhibition of Gastric H+/K+-ATPase by Substituted Imidazo/1, 2-a/pyridines and Related Analogues and Its Implication in Modeling the High Affinity Potassium Ion Binding Site of the Gastric..." page 533 - page 541 --	1-17,20-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 1995	18 -07- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Irja Berlin Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00376

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 32, 1989, J.J. Kaminski et al, "Antiulcer Agents. 4. Conformational Considerations and the Antiulcer Activity of Substituted Imidazol/ 1,2-a/pyridines and Related Analogues", page 1686 - page 1700 -- --------	1-17,20-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE95/00376

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/05/95

International application No.
PCT/SE 95/00376

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4468400	28/08/84	NONE	